Comparison of APTIMA HPV E6/E7 mRNA and Hybrid Capture 2 Assays using Wet and Dry Self-Collected Flocked Vaginal Swabs and PreservCyt L-Pap Samples

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Abstract: *Background*: Performance of HPV assays on less invasive specimens can be assessed through agreement of assays and specimen types as well as the ability to identify patients with precancerous lesions.

Objectives: To compare the APTIMA HPV (AHPV) E6/E7 mRNA assay to the HC2 DNA test for high risk (HR) HPV performed on PreservCyt L-Pap cervical specimens and flocked self-collected vaginal swabs (SCVS) transported to the laboratory wet or dry.

Results: Testing specimens from 100 women attending a colposcopy clinic showed 90.7% (k=0.81) agreement between HC2 and AHPV assays for PreservCyt specimens. Agreement was 80.2% (K=0.80) to 88.0% (K=0.76) between L-Pap and wet and dry SCVS respectively and 89.2% (K=0.77) between the 2 SCVS by AHPV testing. For HC2, the agreement was 90.6% (k=0.81) to 89.2% (k=0.78) between L-Pap and the 2 swabs and 96.0% (k=0.90) between wet and dry swabs. Using pathology (CIN2+) as the reference standard, SCVS tested by AHPV demonstrated sensitivities of 88.8% for dry and 90% for wet SCVS, compared to 86.4% for L-Pap samples. HC2 testing of wet and dry SCVS was 70.8% sensitive compared to 94.4% for L-Pap samples.

Conclusion: SCVS collected with flocked nylon swabs transported wet or dry may serve as alternative specimens for HPV testing of women who are reluctant to have a pelvic examination.

Keywords: HR HPV assays, dry and wet flocked, self-collected vaginal swabs, DNA, mRNA.

1. BACKGROUND

Persistent infection with high risk human papillomavirus (HR HPV) is the primary cause of cervical cancer which affects almost a half a million women worldwide and has a 50% mortality rate [1-3]. Cervical cancer control relies on routine cytology screening with a Pap test to detect and treat women with precursor lesions and immunization of populations at risk. Most women presenting with cervical cancer are not regularly screened with a Pap test [4]. In resource poor settings cytology screening is difficult to implement and in developed countries some women do not regularly receive cytological screening because pelvic examinations may be embarrassing or culturally sensitive. HPV detection is used for the management of women with equivocal cytology results [5, 6] and has been proposed as an alternative primary screening test [7, 8]. Assays for the detection of E6/E7 mRNA have been compared to DNA testing using the APTIMA HPV (AHPV) test [9-13] which detects mRNA of 14 high risk HPV genotypes and the PreTect HPV-Proofer Test which detects mRNA from 5 high risk oncogenic types [12, 14-19]. HR HPV detection is performed using a DNA or E6/E7 mRNA assay on cervical samples collected into liquid medium. There has been great interest in less invasive sampling using self collected specimens [20-34] which women prefer [35-37]. Novel flocked nylon swabs [27] and transportation of dry swabs [38-40] may facilitate HPV testing of SCVS.

2. OBJECTIVES

The objectives of this study were to compare the performance of HR HPV DNA testing Hybrid Capture 2 (HC2) and E6/E7 mRNA testing (APTIMA HPV) on PreservCyt liquid based Pap (L-Pap) fluid collected by a physician and 2 nylon flocked self-collected vaginal swabs (SCVS); one transported in specimen transport media (STM) and the other transported in a dry tube. We measured the presence of HR HPV DNA and E6/E7 mRNA according to sample type and the ability of various combinations of assays and specimens to detect patients with cervical precancerous lesions.

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3. STUDY DESIGN

Sampling and testing: From August 2008 to July 2009 a total of 100 women, ranging in age from 17 to 63 (median age 29) with abnormal Pap tests and attending the Juravinski Hospital Colposcopy Clinic (Hamilton, ON) were enrolled into the study if they had an intact cervix and no history of cervical biopsy or treatment of cervical intraepithelial neoplasia (CIN). Written informed consent was obtained as approved by the McMaster University Research Ethics Committee. Each patient was asked by a nurse whether she would be interested in participating in the study. The nurse explained the study and provided instructions for self-collecting specimens. Each patient opened a package containing 2 flocked nylon swabs (specially designed by Copan Italia, Brescia, Italy) held together by a red cap. For collection, the swabs were held at the midshaft and inserted into the vagina until the patient's fingers touched her vulva. She rotated the swabs 3 times in the vagina, then withdrew them. The patient then gave the swabs to the nurse, who separated them, placing one into a dry transport tube and the other into a tube containing specimen transport media (STM) (Digene HC2 media). The patient was then examined by the colposcopist who obtained an L-Pap sample with a Cervex broom and confirmed that the patients' conditions allowed enrollment into the study. A biopsy was taken if the colposcopist determined that it was warranted. Biopsies were reviewed by pathologists who were blinded to the HPV results. The SCVS were transported to the Infections Research Laboratory (IRL) at St. Joseph's Healthcare, Hamilton and the L-Pap sample was sent to the Pathology Laboratory at the Juravinski Hospital, after which the residual samples were sent to the IRL. The length of time from sample collection to HPV testing ranged from 3 to 10 days.

3.1. HC2 Testing

HC2 DNA testing (Digene/Qiagen) was performed on all samples with sufficient volume. The HC2 assay detects 13 HR oncogenic genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 by hybridization of an RNA probe cocktail with target DNA, capture of RNA/DNA hybrids by antibodies specific for the hybrids and detection with a chemiluminescent substrate. The test was performed according to the package insert using 4mL of the L-Pap sample. Values between 1 and 2 relative light units/ cutoff (RLU/CO) were repeated and values greater than or in this range were considered positive.

3.2. AHPV Testing

The AHPV test was performed at Gen-Probe Inc. in San Diego. The assay detects HPV E6/E7 mRNA from 14 HR oncogenic genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 and was performed as follows: One milliliter of L-Pap fluid was transferred into APTIMA STM; 1mL of residual HC2 STM from each vaginal swab collection was transferred to APTIMA STM following the protocol described by Dockter *et al*. [9].

3.3. Data Analysis

Agreement between tests and between sample types was assessed as raw agreement and as agreement beyond chance (using the Kappa statistics, K). Clinical performance of tests was assessed on the basis of CIN2+ pathology as the endpoint. Sensitivity, specificity and predictive values were calculated using contingency tables and 95% confidence intervals. A p value of < 0.05 was considered statistically significant.

4. RESULTS

A complete set of cervical and vaginal samples were received from 100 women. Because of volume demands for different assays, testing for HR HPV DNA on L-Pap samples by HC2 could not be performed on 14 patients and AHPV E6/E7 mRNA testing could not be performed on 4 L-Pap samples, 14 dry and 9 wet SCVS.

Table **1** shows the agreement between HC2 and AHPV testing of the L-Pap samples. A total of 42

Table 1: Agreement of HC2 and AHPV on PreservCyt L-Pap Samples

	L-Pap (HC2)			
L-Pap (AHPV)		+	-	
	+	42	2	44
	-	6	36	42
		48	38	86

Pos Agreement 84.0% (42/50); Neg Agreement 81.8% (36/44); Overall Agreement 90.7% (78/86) [K=0.81], 95% CI 0.69-0.99.

Table 2: Overall Agreement (%) and Kappa Values between Specimen Types Tested by AHPV or HC2 Assays

Assay	Specimens	SCVS (WET)	SCVS (DRY)
AHPV	L-Pap	80.2 (73/91)(k 0.80)	88.0 (73/83)(k 0.76)
	SCVS (Wet)		89.2 (74/83)(k 0.77)
HC2	L-Pap	90.6 (77/85)(k 0.81)	89.2 (74/83)(k 0.78)
	SCVS (WET)		96.0 (96/100)(k 0.90)

AHPV – APTIMA HPV, HC2 - Hybrid Capture 2, SCVS – Self Collected Vaginal Swab, L-Pap – Liquid Based Pap.

samples contained HR HPV DNA and E6/E7 mRNA. There were 2 samples without HR HPV DNA and another 6 without E6/E7 mRNA. The overall agreement was 90.7% (K=0.81).

Table **2** summarizes agreement of specimen types tested for HR HPV E6/E7 mRNA by AHPV; the strongest agreement was found between wet and dry SCVS, 89.2% (K=0.77), and L-Pap and dry SCVS, 88.0% (K=0.76). In the HC2 test, strongest agreement occurred between dry and wet SCVS, 96% (K=0.90); agreement of L-Pap and wet SCVS was 90.6% (K=0.81) and 89.2% (K=0.78) with dry.

Table **3** compares the various testing strategies for detection of CIN2+ pathology in 24 women. AHPV testing of L-Pap samples was 86.4% compared to 88.2% for either dry or wet SCVS (p=0.48). The AHPV sensitivities were 88.8% for dry and 90.0% for wet (p=0.48). L-Pap testing sensitivities were 94.4% for HC2 compared to 86.4% for AHPV (p=1.0). HC2 testing of the PreservCyt L-Pap samples had a sensitivity of 94.4% compared to HC2 testing of SCVS (dry, wet or both) which was 70.8% sensitive (p=0.25) but there were no differences between dry or wet SCVS (p=1.0). Specificity values for both assays on L-Pap and SCVS were similar.

5. DISCUSSION

This study was designed to determine the feasibility of using self-collected samples to test for HR HPV from women who do not respond to invitations to have a Pap test. In a previous study [38] we compared dry flocked and dry Dacron swabs for cervical and vaginal sampling and demonstrated that flocked swabs detected more HR HPV and more often, from the vagina. When flocked swabs were used in the present study to collect and transport SCVS to the laboratory in a dry or wet state, there was good agreement between the L-Pap samples and SCVS. Agreement ranged from 90.6% (K=0.81) to 89.2% (K=0.78) when tested for DNA by HC2; and 88.0% (K=0.76) to 80.2 (K=0.80) when tested for E6/E7 mRNA by AHPV (Table **2**). Shah *et al*. [39], used a home brew consensus primers-based PCR method and showed strong agreement of physician-collected vaginal swabs transported dry or wet with kappa values ranging from 0.69 to 0.81 but weaker agreement (K=0.37-0.55) between either of the

Table 3: Sensitivity, Specificity and Predictive values for AHPV and HC2 Testing of PreservCyt L-Pap and Dry and Wet Self-Collected Vaginal Swabs (SCVS) to Detect Women with CIN2+ Biopsies

Assay	Specimen	%Sensitivity	% Specificity	%PPV	%NPV
AHPV E6/E7 mRNA	L-Pap	86.4 (19/22)	56.7 (42/74)	37.2 (19/51)	93.3 (42/45)
	Dry VS	88.8 (16/18)	53.9 (41/70)	35.5 (16/45)	95.3 (41/43)
	Wet VS	90.0 (18/20)	46.5 (33/71)	32.1 (18/56)	84.3 (33/35)
	Either	88.2 (15/17)	53.8 (35/65)	33.3 (15/45)	94.6 (35/37)
HC2 DNA	L-Pap	94.4 (17/18)	54.4 (37/68)	35.4 (17/48)	97.4 (37/38)
	Dry VS	70.8 (17/24)	50.0 (38/76)	30.9 (17/55)	84.4 (38/45)
	Wet VS	70.8 (17/24)	50.0 (38/76)	30.9 (17/55)	84.4 (38/45)
	Either	70.8 (17/24)	55.3 (42/76)	33.3 (17/51)	85.7 (42/49)

Comparisons of sensitivities: HC2-dry VS versus wet VS p=1.0; L-Pap versus either dry or wet VS p=0.25; AHPV – dry VS versus wet VS p=0.48; L-Pap versus either dry or wet VS p=0.48; L-Pap HC2 versus AHPV p=1.0.

vaginal samples to cervical samples. A more recent study compared Dacron cervical swabs (CS) transported wet and dry and tested for HR HPV in a realtime TaqMan home brew PCR and genotyping by liquid based microarray [40], showing almost equal numbers of HR HPV positives in the wet and dry samples. The positive agreement was 69.4% (K=0.61), negative agreement was 89.0% (K=0.62) and overall agreement was 91.2%. Agreement and kappa calculations between dry and wet flocked SCVS in the current study were high at 96% (K=0.90) using HC2 and 89.2% (K=0.77) using AHPV (Table **2**).

Although the numbers of CIN2+ cases are limited and restricted volume disallowed all tests to be performed, comparisons of the sensitivity and specificity of cervical samples and SCVS were made. Although there were no statistically significant differences in the sensitivities of each diagnostic approach, AHPV testing of the 3 sample types showed a tight range: L-Pap 86.4%, dry SCVS 88.8% and wet SCVS 90% (Table **3**). The sensitivity for HC2 testing of the L-Pap samples was 94.4% compared to 70.8% for SCVS. These differences suggest that vaginal sampling success may be influenced by different levels of analyte between vaginal and cervical samples and/or differences in analytical sensitivity of the HC2 test (10,000 DNA copies per mL) [41] compared to the AHPV assay (17-488 mRNA copies per mL) [10]. Although the number of patients with negative pathology were small, the specificity values for each specimen type were relatively consistent for both assays. Comparison of the sensitivity of AHPV and HC2 to detect patients with CIN2+ pathology in several published studies from large numbers of women referred because of abnormal Pap results have shown 95.5% versus 99.6% respectively in the United Kingdom [11]; 90.8% versus 95.0% in France [9]; 96.3% versus 94.3% in Canada [12]; and 91.7% versus 91.3% in Germany [13]. Despite limitations of our study including the number of patients with CIN2+ being small and the fact that not all Pap specimens could be tested by HC2, sensitivity trends for the L-Pap samples (AHPV 86.4% versus HC2 94.4%) are similar to 2 of the larger studies [9, 11]. All published comparisons between AHPV and HC2 have shown the specificity of the E6/E7 mRNA APTIMA test to be higher [9, 11-13] for the detection of CIN2+ pathology. Studies comparing the PreTect Proofer Test to HC2 on PreservCyt specimens from patients with CIN2+ have demonstrated similarly higher specificity [12, 14, 16, 17, 19]. Our data reflects a similar trend for most of the specimen types but the number of negatives in our study limits this interpretation.

Agreement data from this study showed that the AHPV E6/E7 mRNA and HC2 DNA assays performed with similar precision on L-Pap and SCVS. The strong agreement of both wet and dry SCVS with L-Pap samples and the high sensitivity of AHPV testing of SCVS and L-Pap samples in patients with CIN2+ lesions demonstrate a need for larger studies using self-collection to test patients for HR HPV.

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